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Dated 20 March 2003

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P01/7700 0.00-0205256.1

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Request for grant of a patent

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1. Your reference P0143-GB01

2. Patent application number *(The Patent Office will fill in this part)* **0205256.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

OXFORD GLYCOSCIENCES (UK) LTD
THE FORUM
86 MILTON PARK
ABINGDON, OXON OX14 4RY
UNITED KINGDOM

Patents ADP number *(if you know it)* 7112386002

If the applicant is a corporate body, give the country/state of its incorporation ENGLAND AND WALES

4. Title of the invention

NOVEL COMPOUNDS

5. Name of your agent *(if you have one)*

BLAKEY, ALISON JANE
OXFORD GLYCOSCIENCES (UK) LTD
THE FORUM
86 MILTON PARK
ABINGDON, OXON OX14 4RY
UNITED KINGDOM

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Patents ADP number *(if you know it)* 7112386002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

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Description	41
Claim(s)	3
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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Allison Bloley Date 6/03/02

12. Name and daytime telephone number of person to contact in the United Kingdom MARY GADSDEN 01235 208127

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NOVEL COMPOUNDS

The present invention relates to novel compounds useful as inhibitors of heparanase, methods for their synthesis, pharmaceutical compositions comprising the novel compounds and their use in medicine, in particular for the treatment of cancer.

The extracellular matrix (ECM) is not only the structural surround for cells in a multicellular organism but also acts as a key modulator and mediator of their physiology, differentiation, organisation and repair. Receptor ligands are stored, concentrated, processed and presented to the cell surface by components of the ECM, which include free and protein-bound heparan sulfate proteoglycans, free and protein-bound chondroitins, collagens, a variety of cell-adhesive integrins such as fibronectin. The ECM is also in a constant flux of degradation and synthesis by neighbouring cells.

The ECM is the principal barrier to tumour growth and metastasis. For a tumour cell to penetrate this barrier it must sufficiently degrade the ECM components so that there is ample space to traverse. The ECM must also be degraded in order to provide avenues for new blood vessel formation in order to supply the increased nutrient requirements of rapidly growing tumors (angiogenesis).

A broad spectrum of degradative enzyme activities are secreted by tumor cells to break down the ECM's complex composition. However, recent studies have demonstrated that inhibiting even just one ECM degrading enzyme appears to provide significant benefit in treating cancer. For example, inhibitors of certain proteases that degrade ECM protein component have been studied in preclinical and clinical trials as anticancer agents.

Carbohydrates represent a large fraction of the total mass of all ECM. Therefore, tumour cells secrete large quantities of carbohydrate degrading enzymes as they penetrate the ECM. In fact, there is good correlation between raised levels of carbohydrate processing enzymes, such as heparanases, secreted by tumour cells and their metastatic potential (e.g., Vlodavsky et al. (1994) *Invasion Metastasis* 14:290-302; (1999) *Nature Medicine* 5:793-802). Heparanases are enzymes that can degrade heparan sulfate as well as heparin and heparan sulfate proteoglycans.

The carbohydrate fragments generated by glycosidase action also promote the cancer phenotype since many are growth-stimulatory. For example, heparanase activity can release heparan sulfate fragments which can increase the potency of a variety of growth factors and heparan sulfate fragments can elicit cell growth stimulation when they are bound by the appropriate cell surface receptors (e.g., Folkman and Shing (1992) *Adv. Exp. Med. Biol.* 313:355-64).

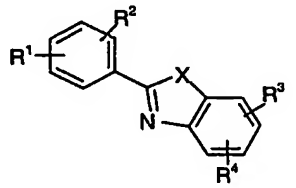
Inhibitors of ECM carbohydrate degradation are potent anticancer agents. For example, sulfated oligosaccharide heparanase inhibitors block tumour metastasis in some animal models (Vlodavsky et al. (1994) *Invasion Metastasis* 14:290-302; Parish et al., (1999) *Cancer Res.* 59:3433-41). Furthermore, heparanase activity results in the release of growth factors that can stimulate angiogenesis and promote tumour growth (Bashkin et al. (1989) *Biochemistry* 28:1737-43).

Heparinomimetic compounds are currently being developed as anticoagulant and antiproliferative agents for the control of thrombotic and proliferative disorders (Demir et al., Clin Appl Thromb Hemost 2001 Apr;7(2):131-40). Thus, a secondary function of heparanase inhibitors may have a role in cardiovascular diseases including blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis.

WO/0135967 discloses the use of heparanase inhibitors for the treatment or prevention of congestive heart failure e.g. primary cardiomyopathy. Associated conditions treated or prevented with the inhibitor are especially peripheral odemas, pulmonary and hepatic congestion, dyspnoea, hydrothorax and ascites. Renal problems, e.g. nocturia can also be treated.

Thus, the present invention provides a class of compounds, which can be used as inhibitors of heparanase. Thus these compounds provide the opportunity for establishing new treatments for cancer, angiogenesis, inflammatory conditions and cardiovascular diseases.

The invention provides a compound of the formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

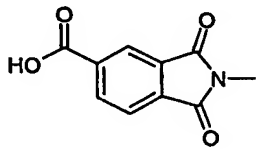


(I)

wherein

X is O or S;

R^1 is a phthalimide carboxylic acid group of formula (II):



(II)

R^2 is hydrogen, halogen, C_1-C_6 alkyl, OR^5 or NR^5R^5 wherein the R^5 substituents together with the nitrogen to which they are attached may form a 5- or 6-membered ring which may contain an additional heteroatom selected from oxygen, nitrogen and sulfur;

R^3 and R^4 are independently hydrogen, halogen, C_1-C_6 alkyl optionally substituted by hydroxy or C_1-C_3 alkoxy, CF_3, OCF_3, OR^{10}, COR^6, $NHCOR^7$, $NHSO_2R^9$, CN, $S(O)_pR^9$, phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^5, COR^6, CN, $NHCOR^7$ and methylenedioxo, or a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur which heteroaromatic ring may be substituted by C_1-C_6 alkyl; or R^3 and R^4 together may form a fused phenyl ring;

R^5 is independently hydrogen, C_3-C_6 alkenyl, C_3-C_6 alkynyl, or C_1-C_6 alkyl optionally substituted by hydroxy, C_1-C_3 alkoxy, NR^7R^8, phenyl optionally substituted by one or more substituents selected from halogen, C_1-C_6 alkyl, CF_3, OCF_3, CN, or a 5- or 6-membered heteroaromatic group optionally substituted by C_1-C_6 alkyl;

R^6 is C_1-C_6 alkyl, OR^5 or NR^7R^8, or phenyl optionally substituted by one or more substituents selected from halogen, C_1-C_6 alkyl, CF_3, OCF_3, OR^5, COR^6, CN, and $NHCOR^7$;

R^7 and R^8 are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl optionally substituted by one or more substituents selected from halogen, CF_3, OCF_3, OR^5, and CN, or a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur which heteroaromatic ring may be substituted by C_1-C_6 alkyl; or R^7 and R^8 together with the nitrogen to which they are attached may form a 5- or 6-membered ring which may contain an additional heteroatom selected from oxygen, nitrogen and sulfur;

R^9 is C_1-C_6 alkyl, or phenyl optionally substituted by one or more substituents selected from halogen, CF_3, OCF_3, OR^5, and CN;

R^{10} is hydrogen, C_3-C_6 alkenyl, C_3-C_6 alkynyl, or C_1-C_6 alkyl optionally substituted by hydroxy or C_1-C_3 alkoxy; and

p is 0, 1 or 2.

The compounds of the invention preferably have a molecular weight of less than 800, more preferably less than 600.

X is preferably O.

When R^2 is NR^5R^5 and the R^5 substituents, together with the nitrogen to which they are attached, form a 5- or 6-membered ring, the ring may be, for example, morpholine.

When R^3 or R^4 is a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur; suitable ring systems include thiophene, benzofuran e.g. 2-benzofuran, benzoxazole e.g. 2-benzoxazole, benzothiazole e.g. 2-benzothiazole, quinoline, isoquinoline, pyridine, pyrimidine, pyrazine, oxadiazole, imidazole, tetrazole, furan and thiophene.

When R^5 is a alkyl optionally substituted by a 5- or 6- membered heteroaromatic group; suitable heteroaromatic groups include, for example furan, thiophene, imidazole, oxadiazole, thiazole, tetrazole, pyridine, pyrimidine and pyrazine.

When R^7 or R^8 is a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur; suitable ring systems include benzofuran, benzoxazole, benzothiazole, quinoline, isoquinoline, oxadiazole, imidazole, tetrazole, furan, and thiophene. It is understood that such a heteroaromatic ring would not contain a N-N link.

The term "alkyl" as used herein whether on its own or as part of a larger group e.g. "alkoxy", includes both straight and branched chain radicals. The term alkyl also includes those radicals wherein one or more hydrogen atoms are replaced by fluorine.

Specific compounds of the invention that may be mentioned include those provided in the examples. A preferred list of specific compounds of the invention include:

2-[3-(Naphth[2,3-d]oxazol-2-yl)phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

2-[3-(5-Chlorobenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-(5-phenylbenzoxazol-2-yl)-phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[(5-benzofuran-2-yl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3,4-methylenedioxyphenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-chlorophenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3,4-dichloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3-chloro-4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-methyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3-chloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(2,4-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(3,5-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

Suitable pharmaceutically acceptable salts of the compounds include those derived from inorganic and organic bases. Examples of suitable inorganic bases include the hydroxides, carbonates, and bicarbonates of ammonia, lithium, sodium, calcium, potassium, aluminium, iron, magnesium, zinc and the like. Salts can also be formed with suitable organic bases. Such organic bases are well known in the art and may include amino acids such as arginine and lysine, mono-, di-, or trihydroxyalkylamines such as mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and trimethylamine, guanidine; N-methylglucosamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl) aminomethane; and the like.

Salts may be prepared in a conventional manner using methods well known in the art, for example by treatment of a solution of the compound of formula (I) with a solution of the base, for example, potassium or sodium hydroxide, or potassium or sodium hydrogen carbonate.

The invention also includes prodrugs of the aforementioned compounds. A prodrug is commonly described as an inactive or protected derivative of an active ingredient or a drug, which is converted to the active ingredient or drug in the body. Examples of prodrugs include pharmaceutically acceptable esters, including C_1-C_6 alkyl esters and pharmaceutically acceptable amides, including secondary C_1-C_3 alkylamides.

In addition, the invention extends to active derivatives of the aforementioned compounds.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

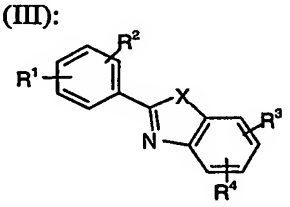
Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. Where a compound contains an alkene moiety, the alkene can be presented as a cis or trans isomer or a mixture thereof. When an isomeric form of a compound of the invention is provided substantially free of other isomers, it will preferably contain less than 5% w/w, more preferably less than 2% w/w and especially less than 1% w/w of the other isomers.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

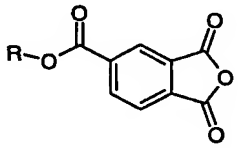
The invention also provides a process for preparing a compound of formula (I), comprising:

treating a compound of formula (III):



(III)

wherein R^1 is NH_2 or protected derivative thereof and X, R^2, R^3 and R^4 are as defined for formula (I), with a compound of formula (IV):



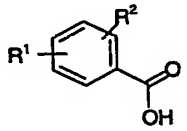
(IV)

wherein R is H, C_1-C_6 alkyl e.g. CH_3, C_2H_5, or a protecting group e.g. CH_2Ph, by heating in a suitable acidic medium for example in a solution of acetic acid or other suitable organic acid. Alternatively, compounds of the invention may be prepared by heating a compound of formula (III) and a

compound of formula (IV) with an organic base, for example triethylamine in a suitable solvent, for example dimethylformamide, followed by heating in a suitable acidic medium, for example acetic acid.

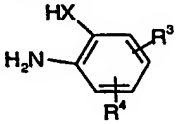
The compounds where R is C_1-C_6 alkyl or a protecting group may be converted to the compounds of formula (I) where R is H using methods well known to those skilled in the art, for example hydrolysis with sodium hydroxide in water, or hydrogenation (where R = CH_2Ph) with palladium on charcoal catalyst/hydrogen. Certain basic conditions may cause phthalimide ring cleavage, re-cyclisation can then be carried out using the acidic conditions described above.

A compound of formula (III) where R^1 is NH_2 may be prepared from a corresponding compound where R^1 is NO_2 by methods well known to those skilled in the art, for example hydrogenation with palladium on charcoal catalyst. The compounds where R^1 is NO_2 may be prepared by treatment of a compound of formula (V):



(V)

wherein R^1 is NO_2 and R^2 is as defined for formula (I), with a compound of formula (VI):

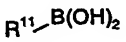


(VI)

wherein X, R^3 and R^4 are as defined for formula (I), by heating in a condensation/cyclisation reaction using for example polyphosphoric acid or alternatively by firstly coupling a compound of formula (VI) to a compound of formula (V) via either an ester/ thioester or amide formation reaction using methods well known to those of skill in the art followed by direct heating or heating with an acidic media with a suitable solvent to effect cyclisation, for example p-toluenesulfonic acid in toluene. Alternatively this may be achieved via oxidative cyclisation of a Schiff base, derived from the condensation of the 2-aminophenol or 2-aminothiophenol and aldehydes, using various oxidants such as $PhI(OAc)_2$, $Pb(OAc)_4$ or DDQ.

Compounds of formulae (V) and (VI) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

The compounds of formula (III) where R^1 is NO_2, R^2 is as defined in formula (I) and R^3 or R^4 are halo, may be further modified by a coupling reaction with compounds of formula (VII) using an appropriate catalyst for example tetrakis (triphenylphosphine) palladium:



(VII)

wherein R^{11} is a phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^5, COR^6, CN, $NHCOR^7$ and methylenedioxo, or a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur which heteroaromatic ring may be substituted by C_1-C_6 alkyl. Similarly, the compounds where R^1 is NO_2,

R^2 is OR^5 or NR^5R^5 and R^3 or R^4 are independently $B(OH)_2$ a similar palladium coupling reaction with halo aromatic compounds may be used.

Compounds of formula (III) where R^1 is NO_2, R^2 is halo and R^3 and R^4 are as defined in formula (I) may be converted to another compound of formula (III) where R^2 is as defined in formula (I) by reaction with an alcohol or amine via a nucleophilic aromatic substitution or by a coupling reaction with compounds of formula (VII) as described above.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry,* T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts and prodrugs thereof.

Any novel intermediate compounds as described herein also fall within the scope of the present invention.

The pharmaceutically effective compounds of formula (I) and pharmaceutically acceptable salts and prodrugs thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") with standard pharmaceutical carriers or excipients according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, together with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318, (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, impregnated dressings, sprays, aerosols or oils and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

For applications to the eye or other external tissues, for example the mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The pharmaceutical formulations according to the invention are preferably adapted for oral administration.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. Such a unit may contain for example 100mg/kg to 1mg/kg depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the compound of formula (I) given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The compounds of the present invention are useful in that they are capable of inhibiting heparanase. Thus, the compounds can be used in the treatment of cancers, preferably the treatment of metastatic tumour cells. Examples of such types of cells include melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma and mastocytoma. Types of cancer include colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, renal cancer, gastric cancer, bladder cancer and ovarian cancer.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for cancer. Examples of such treatments include, surgery and radiation therapy. Examples of therapeutic compounds include but are not limited to cyclophosphamide (Cytoxan™); methotrexate (Methotrexate™); 5-fluorouracil (5-FU); paclitaxel (Taxol™); docetaxel (Taxotere™); vincristine (Oncovin™); vinblastine (Velban™); vinorelbine (Navelbine™); doxorubicin (Adriamycin™); tamoxifen (Nolvadex™); toremifene(Fareston™); megestrol acetate(Megace™); anastrozole (Arimidex™); goserelin (Zoladex™); anti-HER2 monoclonal antibody (Herceptin™); capecitabine (Xeloda™) and raloxifene hydrochloride (Evista™).

The compounds of the present invention can also be used in the treatment of angiogenesis and angiogenesis dependent diseases which include angiogenesis associated with the growth of solid tumours and retinopathy.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for angiogenesis. Examples of such other therapeutic compounds include but are not limited to recombinant platelet-derived growth factor-BB (Regranex™).

The compounds of the present invention can also be used in the treatment of inflammatory conditions including but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing.

The compounds of the present invention can also be used in the treatment of cardiovascular diseases such as but not limited to blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis.

By the term "treating" is meant either prophylactic or therapeutic therapy.

In additional aspects, therefore, the present invention provides:

(i) the use of a compound of formula (I) as an inhibitor of the enzyme heparanase.

(ii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cancers, preferably the treatment of metastatic tumour cells. Examples of such types of cells include melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma and mastocytoma. Types of cancer include but

are not limited to, colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, renal cancer, gastric cancer, bladder cancer and ovarian cancer.
(iii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of angiogenesis and angiogenesis dependent diseases which include angiogenesis associated with the growth of solid tumours and retinopathy.
(iv) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of inflammatory conditions such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing.
(v) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cardiovascular diseases such as but not limited to blood clotting conditions, for example thromoembolic disease, arterial thrombosis and restenosis.
(vi) a method for the treatment of cancers, preferably the treatment of metastatic tumour cells which comprises the step of administering to a patient an effective amount of a compound of formula (I).
(vii) a method for the treatment of angiogenesis and angiogenesis dependent diseases, which include angiogenesis associated with the growth of solid tumours and retinopathy, which comprises the step of administering to a patient an effective amount of a compound of formula (I).
(viii) a method for the treatment of inflammatory diseases, such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing which comprises the step of administering to a patient an effective amount of a compound of formula (I).
(ix) a method for the treatment of cardiovascular diseases, such as but not limited to blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis which comprises the step of administering to a patient an effective amount of a compound of formula (I).

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

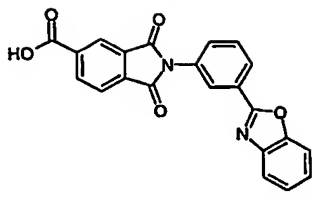
The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Example 1: 2-[3-(Benzoxazol-2-yl)phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Aminophenyl) benzoxazole

3-Aminobenzoic acid (500mg, 3.65mmol) and 2-aminophenol (398mg, 3.65mmol) were mixed with polyphosphoric acid (5ml). The reaction was heated to 200°C for 4h. The reaction mixture was slowly poured into ice water (100ml) and the resulting mixture basified with solid sodium hydroxide. At pH5-6 the precipitate was filtered, washed with water and dried to give the subtitle compound, 625mg (82%). ^{1}H NMR ($CDCl_3$) δ 7.78(m, 1H), 7.65(d, J=7.5Hz, 1H) 7.59(m, 2H), 7.36(m, 3H), 6.86(dd, J=2.2, 7.9Hz, 1H). MS: 211m/z $(M+H)^+$.

b) 2-[3-(Benzoxazol-2-yl)phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



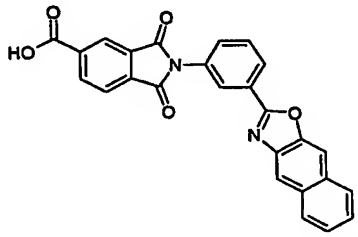
2-(3-Aminophenyl)benzoxazole (500mg, 2.4mmol) and 1,2,4-benzenetricarboxylic anhydride (546mg, 2.4mmol) in acetic acid (25ml) were heated to reflux overnight. On cooling the precipitate was filtered, washed with acetic acid and dried to give the title compound 710mg (71%). ^{1}H NMR ($CDCl_3$) δ 8.44(dd, J=1.5, 7.9Hz, 1H), 8.36(d, J=4.5Hz, 2H) 8.28(dt, J=1.5, 7.2Hz, 1H), 8.12(d, J=7.9Hz, 1H), 7.86-7.39(m, 4H), 7.45(m, 2H). MS: 383m/z $(M-H)^-$.

Example 2: 2-[3-(Naphth[2,3-d]oxazol-2-yl)phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Aminophenyl)naphth[2,3-d]oxazole

Prepared by the method of Example 1a) from 3-amino-2-naphthol (579mg, 3.6mmol) and 3-aminobenzoic acid (500mg, 3.6mmol) the subtitle compound was obtained, 58mg (6%). ^{1}H NMR ($CDCl_3$) δ 8.12(s, 1H), 7.90(m, 3H), 7.65(dt, J=1.5, 7.5Hz, 1H), 7.60(t, J=2.3Hz, 1H), 7.42(m, 2H), 7.27(t, J=7.9Hz), 6.82(dd J=2.3, 7.9Hz). MS: 261 m/z $(M+H)^+$.

b) 2-[3-(Naphth[2,3-d]oxazol-2-yl)phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



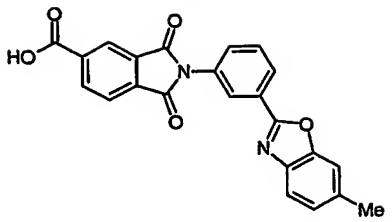
Prepared by the method of Example 1b) from 2-(3-aminophenyl)naphth[2,3-d]oxazole (36mg, 0.14mmol) and 1,2,4-benzenetricarboxylic anhydride (30mg, 0.16mmol) the title compound was obtained, 30mg (44%). ^{1}H NMR (DMSO) δ 8.45(m, 2H), 8.38(d, 3H), 8.30(s, 1H), 8.12(m, 3H), 7.82(m, 2H), 7.55(m, 2H). MS: 433m/z $(M-H)^-$.

Example 3: 2-[3-(6-Methylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Aminophenyl)-6-methylbenzoxazole

Prepared by the method of Example 1a) from 2-amino-5-methylphenol (448mg, 3.6mmol) and 3-aminobenzoic acid (500mg, 3.6mmol) the subtitle compound was obtained, 97mg (12%). ^{1}H NMR ($CDCl_3$) δ 7.55(d, J=8.2Hz, 2H), 7.49(t, J=1.9Hz, 1H), 7.30(s, 1H), 7.22(t, J=7.5Hz, 1H), 7.08(dd, J=1.1, 8.2Hz, 1H), 6.76(dd, J=2.3, 7.9Hz, 1H), 2.43(s, 3H). MS: 225m/z $(M+H)^+$.

b) 2-[3-(6-Methylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



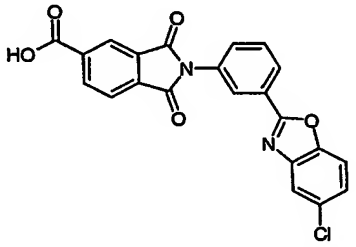
Prepared by the method of Example 1b) from 2-(3-aminophenyl)-6-methylbenzoxazole (32mg, 0.14mmol) and 1,2,4-benzenetricarboxylic anhydride (30mg, 0.16mmol) the title compound was obtained, 42mg (72%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.34(bd, 2H), 8.25(dt, 1H), 8.13(d, 1H), 7.75(m, 3H), 7.63(s, 1H), 7.26(d, 1H), 2.50(s, 3H). MS: 397m/z $(M-H)^-$.

Example 4: 2-[3-(5-Chlorobenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Aminophenyl)-5-chlorobenzoxazole

Prepared by the method of Example 1a) from 2-amino-4-chlorophenol (522mg, 3.6mmol) and 3-aminobenzoic acid (500mg, 3.6mmol) the subtitle compound was obtained, 114mg (13%). ^{1}H NMR ($CDCl_3$) δ 7.81(bs, 1H), 7.69-7.60(m, 5H), 7.49(t, J=7.1Hz), 7.41-7.27(m, 3H), 6.96(dd, J=2.6, 7.9Hz, 1H). MS: 245, 247m/z $(M+H)^+$.

b) 2-[3-(5-Chlorobenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



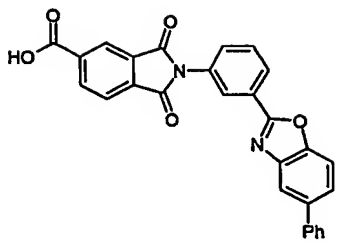
Prepared by the method of Example 1b) from 2-(3-aminophenyl)-5-chlorobenzoxazole (34mg, 0.14mmol) and 1,2,4-benzenetricarboxylic anhydride (30mg, 0.16mmol) the title compound was obtained, 38mg (64%). ^{1}H NMR (DMSO) δ 8.48(dd, 1H), 8.39(bd, 2H), 8.30(dt, 1H), 8.16(d, 1H), 8.00(d, 1H), 7.88(m, 4H), 7.54(dd, 1H). 417MS: 417m/z $(M-H)^-$.

Example 5: 2-[3-(5-Phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Aminophenyl)-5-phenylbenzoxazole

Prepared by the method of Example 1a) from 2-amino-4-phenylphenol (674mg, 3.6mmol) and 3-aminobenzoic acid (500mg, 3.6mmol) the subtitle compound was obtained, 84mg (8%). ^{1}H NMR ($CDCl_3$) δ 7.97(bs, 1H), 7.70-7.57(m,3H), 7.45-7.35(m, 2H), 6.96(d, J=7.9Hz, 1H). MS: 287m/z $(M+H)^+$.

b) 2-[3-(5-Phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



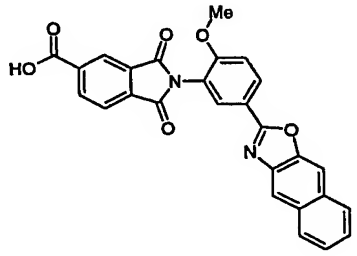
Prepared by the method of Example 1b) from 2-(3-aminophenyl)-5-phenylbenzoxazole (40mg, 0.14mmol) and 1,2,4-benzenetricarboxylic anhydride (30mg, 0.16mmol) the title compound was obtained, 45mg (70%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38(d, 2H), 8.30(dt, 1H), 8.12(m, 2H), 7.9(d, 1H), 7.78(m, 5H), 7.51(t, 2H), 7.40(t, 1H). MS: 459m/z $(M-H)^-$.

Example 6: 2-[2-Methoxy-5-(naphth[2,3-d]oxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methoxyphenyl)-naphth[2,3-d]oxazole

Prepared by the method of Example 1a) from 3-amino-2-naphthol (476mg, 2.9mmol) and 4-methoxy-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 120mg (14%). ^{1}H NMR ($CDCl_3$) δ 8.06(s, 1H), 7.92-7.83(m, 3H), 7.67(dd, J=1.9, 8.2Hz, 1H), 7.60(d, J=1.9Hz, 1H), 7.38(m, 2H), 6.85(d, J=8.3Hz, 1H), 3.88(s, 3H). MS: 291m/z $(M+H)^+$.

b) 2-[2-Methoxy-5-(naphth[2,3-d]oxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



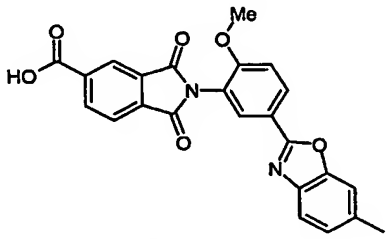
Prepared by the method of Example 1b) from 2-(3-amino-4-methoxyphenyl)-naphth[2,3-d]oxazole (67mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride (50mg, 0.26mmol) the title compound was obtained, 40mg (37%). ^{1}H NMR (DMSO) δ 8.34(m, 4H), 8.24(d, 1H), 8.15(s,1H), 8.01(m, 3H), 8.43(m, 3H), 3.81(s, 3H). MS: 463m/z $(M-H)^-$.

Example 7: 2-[2-Methoxy-5-(6-methylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methoxyphenyl)-6-methylbenzoxazole

Prepared by the method of Example 1a) from 2-amino-5-methylphenol (368mg, 2.9mmol) and 4-methoxy-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 75mg (10%). ^{1}H NMR ($CDCl_3$) δ 7.69-7.58(m, 4H), 7.35(bs, 1H), 6.92(d, J=7.9Hz), 3.85(s, 3H), 2.51(s, 3H). MS: 255m/z $(M+H)^+$.

b) 2-[2-Methoxy-5-(6-methylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



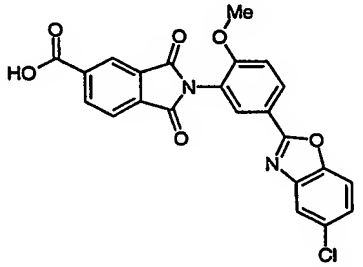
Prepared by the method of Example 1b) from 2-(3-amino-4-methoxyphenyl)-6-methylbenzoxazole (58mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride (50mg, 0.26mmol) the title compound was obtained, 54mg (55%). ^{1}H NMR (DMSO) δ 8.31(dd, 1H), 8.16(m, 3H), 7.97(d, 1H), 7.50(d, 1H), 7.43(s, 1H), 7.32(d, 1H), 7.08(d, 1H), 3.73(s, 3H), 2.33(s, 3H). MS: 427m/z $(M-H)^-$.

Example 8: 2-[2-Methoxy-5-(5-chlorobenzoxazolyl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methoxyphenyl)-5-chlorobenzoxazole

Prepared by the method of Example 1a) from 4-chloro-2-aminophenol (429mg, 2.9mmol) and 4-methoxy-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 111mg (10%). ^{1}H NMR ($CDCl_3$) δ 7.70(d, J=1.9Hz, 1H), 7.65(dd, J=1.9, 8.3Hz, 1H), 7.59(d, J=1.9Hz, 1H), 7.46(d, J=8.3Hz, 1H), 7.28(dd, J=1.9, 8.3Hz, 1H), 6.90(d, J=8.3Hz, 1H), 3.96 (s, 3H). MS: 275m/z $(M+H)^+$.

b) 2-[2-Methoxy-5-(5-chlorobenzoxazolyl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



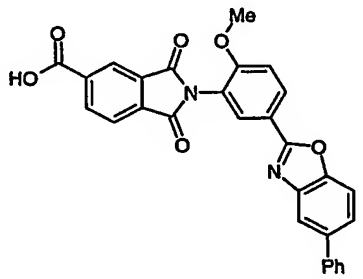
Prepared by the method of Example 1b) from 2-(3-amino-4-methoxyphenyl)-5-chlorobenzoxazole (63mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride (50mg, 0.26mmol) the title compound was obtained, 62mg (60%). ^{1}H NMR (DMSO) δ 8.45 (dd, 1H), 8.33 (m, 3H), 8.12 (d, 1H), 7.89 (d, 1H), 7.80 (d, 1H), 7.47 (m, 2H), 3.89 (s, 3H). MS: 447m/z $(M-H)^-$.

Example 9: 2-[2-Methoxy-5-(5-phenylbenzoxazol-2-yl)-phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methoxyphenyl)-5-phenylbenzoxazole

Prepared by the method of Example 1a) from 2-amino-4-phenylphenol (554mg, 2.9mmol) and 4-methoxy-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 111mg (10%). ^{1}H NMR ($CDCl_3$) δ 7.84(s, 1H), 7.72-7.38(m, 9H), 6.93(d, J=8.3Hz, 1H), 3.96(s, 3H). MS: 316m/z $(M+H)^+$.

b) 2-[2-Methoxy-5-(5-phenylbenzoxazol-2-yl)-phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



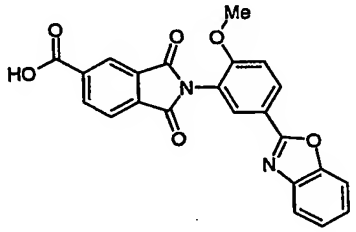
Prepared by the method described in Example 1b) from 2-(3-amino-4-methoxyphenyl)-5-phenylbenzoxazole (73mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride (50mg, 0.26mmol) the title compound was obtained, 50mg (44%). ^{1}H NMR (DMSO) δ 8.46(dd, 1H), 8.35(m, 3H), 8.13(d, 1H), 8.03(d, 1H), 7.84(d, 1H), 7.73(m, 3H), 7.49(m, 3H), 7.39(t, 1H), 3.90(s, 3H). MS: 489m/z $(M-H)^-$.

Example 10: 2-[2-Methoxy-5-(benzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methoxyphenyl)-benzoxazole

Prepared by the method of Example 1a) from 2-aminophenol (326mg, 2.9mmol) and 4-methoxy-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 97mg (13%). ^{1}H NMR ($CDCl_3$) δ 7.66-7.45(m, 4H), 7.24(m, 2H), 6.82(d, J=8.3Hz, 1H), 3.86(s, 3H). MS: 241m/z $(M+H)^+$.

b) 2-[2-Methoxy-5-(benzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



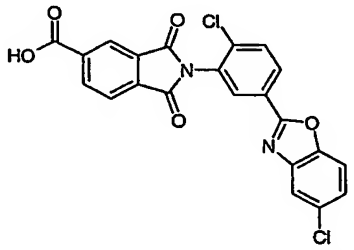
Prepared by the method of Example 1b) from 2-(3-amino-4-methoxyphenyl)benzoxazole (55mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride (50mg, 0.26mmol) the title compound was obtained, 64mg (67%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.32(m, 3H), 8.12(d, 1H), 7.78(m, 2H), 7.49(d, 1H), 7.41(m, 2H), 3.88(s, 3H). MS: 413m/z $(M-H)^-$.

Example 11: 2-[2-Chloro-(5-chlorobenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-6-chlorophenyl)-5-chlorobenzoxazole

Prepared by the method of Example 1a) from 4-chloro-2-aminophenol (861mg, 6.0mmol) and 4-chloro-3-aminobenzoic acid (1g, 6.0mmol) the subtitle compound was obtained, 1.57g (97%). ^{1}H NMR ($CDCl_3$) δ 7.73(d, J=2.3Hz, 1H), 7.65(d, J=1.9Hz, 1H), 7.55(dd, J=2.3Hz, 1H), 7.49(d, 1H), 7.33(dd, 1H). MS: 279, 281m/z $(M+H)^+$.

b) 2-[2-Chloro-(5-chlorobenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



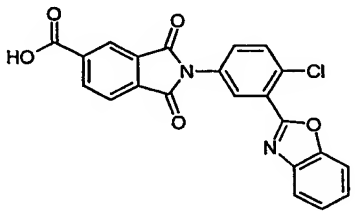
Prepared by the method of Example 1b) from 2-(3-amino-6-chlorophenyl)-5-chlorobenzoxazole (327mg, 1.2mmol) and 1,2,4-benzenetricarboxylic anhydride (250mg, 1.3mmol) the title compound was obtained, 180mg (31%). ^{1}H NMR (DMSO) δ 8.33(d, 1H), 8.25(dd, 1H), 8.16(bs, 1H), 8.12(dd, 1H), 7.95(d, 1H), 7.77(d, 1H), 7.74(d, 1H), 7.63(d, 1H). MS: 451, 452m/z $(M-H)^-$.

Example 12: 2-[4-Chloro-(5-phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(2-Chloro-5-aminophenyl)benzoxazole

Prepared by the method of Example 1a) from 2-aminophenol (318mg, 2.9mmol) and 4-chloro-3-aminobenzoic acid (500mg, 2.9mmol) the subtitle compound was obtained, 583mg (82%). ^{1}H NMR ($CDCl_3$) δ 7.81(t, 1H), 7.59(t, 1H), 7.44(d, 1H), 7.36(d, 1H), 7.29(d, 1H), 6.74(dd, 2H). MS: 245m/z $(M+H)^+$.

b) 2-[4-Chloro-(5-phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 1b) from 2-(2-chloro-5-aminophenyl)benzoxazole (250mg, 1.0mmol) and 1,2,4-benzenetricarboxylic anhydride (196mg, 1.0mmol) the title compound was obtained, 350mg (82%). ^{1}H NMR (DMSO) δ 8.50(dd, 1H), 8.42(m, 2H), 8.18(d, 1H), 7.96(m, 3H), 7.83(dd, 1H), 7.56(m, 2H). MS: 417m/z $(M-H)^-$.

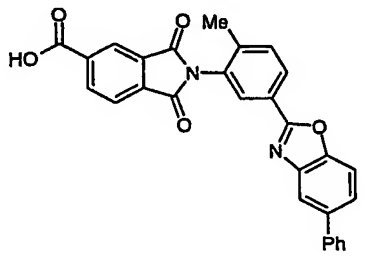
Example 13: 2-[2-Methyl-5-(5-phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methylphenyl)-4-phenylbenzoxazole

Prepared by the method of Example 1a) from 2-amino-4-phenylphenol (1.23g, 7.0mmol) and 3-amino-4-methylbenzoic acid (1.00g, 7.0mmol) the subtitle compound was obtained, 814mg (41%). ^{1}H NMR

(DMSO) δ 8.01(d, 1H), 7.82(d, 1H), 7.73(m, 2H), 7.67(dd, 1H), 7.49(m, 3H), 7.40(d, 1H), 7.34(dd, 1H), 7.15(d, 1H), 2.50(s, 3H). MS: 301m/z $(M+H)^+$.

b) 2-[2-Methyl-5-(5-phenylbenzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



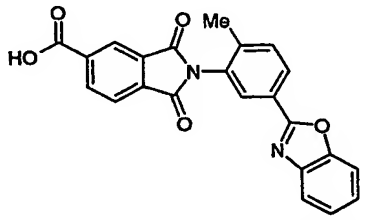
Prepared by the method of Example 1b) from 2-(3-amino-4-methylphenyl)-4-phenylbenzoxazole (167mg, 0.9mmol) and 1,2,4-benzenetricarboxylic anhydride (250mg, 0.9mmol) the title compound was obtained, 340mg (82%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.34(d, 2H), 8.26(dd, 1H), 8.13(d, 1H), 8.05(nd, 1H), 7.85(d, 1H), 7.73(m, 4H), 7.50(t, 1H), 7.39(t, 1H), 2.28(s, 3H). MS: 473m/z $(M-H)^-$.

Example 14: 2-[2-Methyl-5-(benzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid

a) 2-(3-Amino-4-methylphenyl)-benzoxazole

Prepared by the method of Example 1a) from 2-aminophenol (720mg, 7.0mmol) and 3-amino-4-methylbenzoic acid (1.00g, 7.0mmol) the subtitle compound was obtained, 942mg (57%). ^{1}H NMR (DMSO) δ 7.67(m, 2H), 7.42(s, 1H), 7.31(m, 2H), 7.24(d, 1H), 7.07(d, 1H), 2.43(s, 3H). MS: 225m/z $(M+H)^+$.

b) 2-[2-Methyl-5-(benzoxazol-2-yl)-phenyl]-2,3-dihydro-1,3-dioxo-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 1b) from 2-(3-amino-4-methylphenyl)-benzoxazole (250mg, 1.1mmol) and 1,2,4-benzenetricarboxylic anhydride (214mg, 1.1mmol) the title compound was obtained. 375mg (84%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.33(d, 2H), 8.23(dd, 1H), 8.12(d, 1H), 7.79(m, 2H), 7.68(d, 1H), 7.44(m, 2H). MS: 397m/z $(M-H)^-$.

Example 15: 2-[2-Methoxy-5-[(5-benzofuran-2-yl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

a) 4-Methoxy-3-nitro-benzoyl chloride

Oxalyl chloride (15.8ml, 180mmol) was added dropwise with stirring to a solution of 4-methoxy-3-nitrobenzoic acid (7.00g, 36.00mmol) in THF containing 10μL DMF. After 1h the solvent was removed under reduced pressure. The product was used directly in the next step.

b) 2-(4-Methoxy-3-nitrophenyl)-amido-4-bromophenol

A solution of 4-methoxy-3-nitro-benzoyl chloride (7.12g, 33.0mmol) in THF (50 ml) was added dropwise with stirring to a solution of 4-bromo-2-aminophenol (6.20g, 33.0mmol) in THF (50ml) containing triethylamine (6.82ml, 66.0mmol). After addition was complete the reaction was stirred at room temperature overnight. The reaction mixture was concentrated to approximately half the original volume and the precipitate collected by filtration. The solid was washed with methanol and ether and dried under vacuum to give the subtitle compound as a brown solid (5.24g, 42%). ^{1}H NMR (DMSO) δ 8.58(d, 1H), 8.36(dd, 1H), 7.55(d, 1H), 6.96(m, 2H), 6.68(dd, 1H), 4.05(s, 3H).

c) 2-(3-Nitro-4-methoxyphenyl)-5-bromobenzoxazole

A suspension of 2-(4-methoxy-3-nitrophenyl)-amido-4-bromophenol (5.24g, 14.2mmol) and toluenesulfonic acid (5.36g, 31.2mmol) in toluene (100ml) was heated to reflux overnight. The cooled reaction mixture was washed with saturated sodium hydrogen carbonate solution (care foaming) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2x50ml) and the combined organic layers dried over sodium sulfate and the solvent removed under reduced pressure. The residue was triturated with ether, filtered and dried under vacuum to give the subtitle compound as a pale pink solid (4.51g, 93%). ^{1}H NMR (DMSO) δ 8.61(d, 1H), 8.42(dd, 1), 8.05(d, 1H), 7.79(d, 1H), 7.61(m, 2H), 4.05(s, 3H). MS m/z 349.0 $(M+H)^+$.

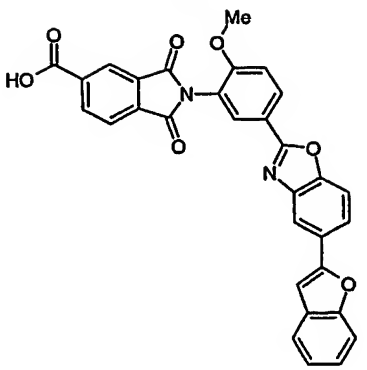
d) 2-(3-Nitro-4-methoxyphenyl)-5-(benzofuran-2-yl)benzoxazole

2-(3-Nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) was suspended in degassed ethylene glycol dimethyl ether (DME, 10ml). Tetrakis (triphenylphosphine)palladium (0) (33mg, 0.03mmol), 2M sodium carbonate (0.5ml) and benzofuran-2-boronic acid (137mg (0.85mmol) were added and the reaction was further degassed. The reaction was heated to reflux for 16h. The cooled reaction mixture was diluted with water (10ml) and extracted with dichloromethane (2x10ml). The combined organic extracts were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was triturated with methanol (5ml) and filtered. The solid was dried under vacuum to give the subtitle compound (50mg, 15%). ^{1}H NMR (DMSO) δ 8.63(d, 1H), 8.44(dd, 1H), 8.29(d, 1H), 8.01(dd, 1H), 7.92(d, 1H), 7.69-7.59(m, 3H), 7.54(s, 1H), 7.36-7.25(m, 2H), 4.04(s, 3H).

e) 2-(3-Amino-4-methoxyphenyl)-5-(benzofuran-2-yl)benzoxazole

A suspension of 2-(3-nitro-4-methoxyphenyl)-5-(benzofuran-2-yl)benzoxazole (50mg, 0.13mmol) in dioxane (10ml) was placed under an atmosphere of argon. Palladium on carbon (10%) (10mg) was added and the reaction purged with hydrogen and stirred at room temperature for 36h. The reaction was filtered through a bed of celite and the filtrate concentrated to give the subtitle compound (40mg, 86%). MS m/z 357.1 $(M+H)^+$.

f) 2-[2-Methoxy-5-[(5-benzofuran-2-yl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



2-(3-Amino-4-methoxyphenyl-5-(benzofuran-2-yl)benzoxazole (40mg, 0.11mmol) and 1,2,4-benzenetricarboxylic anhydride (23mg, 0.12mmol) in acetic acid (5ml) were heated to reflux overnight. On cooling the precipitate was filtered, washed with acetic acid and dried under vacuum to give the title compound (30mg, 51%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.35(m, 3H), 8.29(d, 1H), 8.13(dd, 1H), 8.00(dd, 1H), 7.90(d, 1H), 7.67(m, 2H), 7.55(s, 1H), 7.50(d, 1H), 7.36-7.25(m, 2H), 3.89(s, 3H). MS m/z 528.6 $(M+H)^+$.

Example 16: 2-[2-Methoxy-5-[5-(3-acetyl)phenylbenzoxazol-2yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

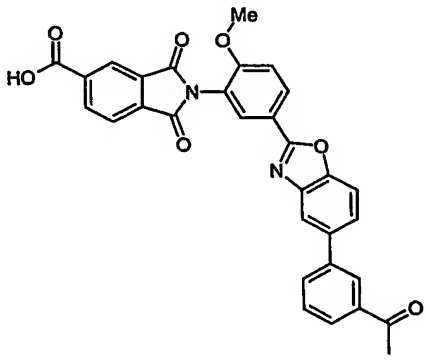
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-acetylphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-acetylphenylboronic acid (139mg, 0.85mmol) the subtitle compound was obtained (89mg, 26%). ^{1}H NMR (DMSO) δ 8.75(d, 1H), 8.46(dd, 1H), 8.23(t, 1H), 7.98-7.96(m, 2H), 7.69-7.56(m, 3H), 7.27(d, 1H), 4.08(s, 3H), 2.68(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-acetylphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-acetylphenyl)-benzoxazole (89mg, 0.23mmol) the subtitle compound was obtained (80mg, 97%). MS m/z 359.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(3-acetyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl-5-(3-acetylphenyl)benzoxazole (80mg, 0.22mmol) and 1,2,4-benzenetricarboxylic anhydride (47mg,

0.25mmol) the title compound was obtained (84mg, 71%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.39-8.33(m, 3H), 8.26(s, 1H), 8.26(t, 1H), 8.14-8.11(m, 2H), 8.01(d, 1H), 7.96(d, 1H), 7.88(d, 1H), 7.78(dd, 1H), 7.65(t, 1H), 7.50(d, 1H). MS m/z 533.0 $(M+H)^+$.

Example 17: 2-[2-Methoxy-5-[5-(3,4-methylenedioxyphenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

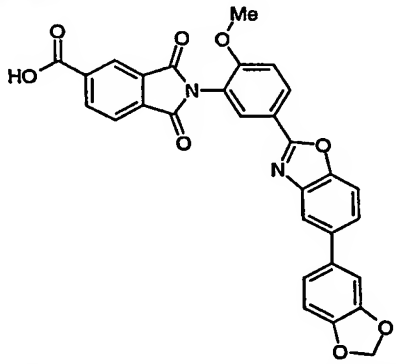
a) 2-(3-Nitro-4-methoxyphenyl)-5-[3,4-(methylenedioxy)phenyl]benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3,4-methylenedioxyboronic acid (141mg, 0.85mmol) the subtitle compound was obtained (127mg, 38%). ^{1}H NMR (DMSO) δ 8.63(d, 1H), 8.45(dd, 1H), 7.99(d, 1H), 7.82(d, 1H), 7.82(dd, 1H), 7.62(d, 1H), 7.33(d, 1H), 7.21(dd, 1H), 7.02(d, 1H), 6.08(s, 2H), 4.05(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-[3,4-(methylenedioxy)phenyl]benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3,4-[methylenedioxy]phenyl)-benzoxazole (135mg, 0.35mmol) the subtitle compound was obtained (120mg, 95%) MS m/z 361.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(3,4-methylenedioxyphenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl-5-[3,4-(methylenedioxy)phenyl]benzoxazole (120mg, 0.33mmol) and 1,2,4-benzenetricarboxylic anhydride (70mg, 0.36mmol) the title compound was obtained (82mg, 46%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.37-8.32(m, 3H), 8.12(d, 1H), 7.96(d, 1H), 7.79(d, 1H), 7.63(dd, 1H), 7.49(d, 1H), 7.33(d, 1H), 7.20(dd, 1H), 7.02(d, 1H), 6.06(2H, s), 3.88(s, 3H). MS m/z 535.0 $(M+H)^+$.

Example 18: 2-[2-Methoxy-5-[5-(4-chlorophenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

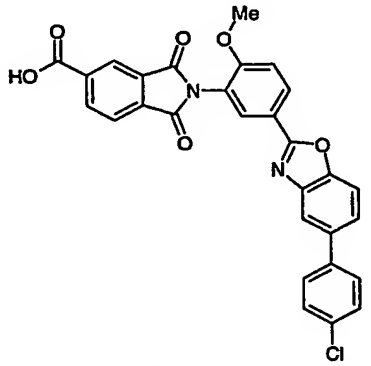
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-chlorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-chlorophenylboronic acid (134mg, 0.85mmol) the subtitle compound was obtained (148mg, 68%). ^{1}H NMR ($CDCl_3$) δ 8.74(s, 1H), 8.45(dd, 1H), 7.90(d, 1H), 7.64(d, 1H), 7.55(d, 3H), 7.44(d, 2H), 7.26(d, 1H), 4.07(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-chlorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(4-chlorophenyl)-benzoxazole (134mg, 0.35mmol) the subtitle compound was obtained (104mg, 85%). MS m/z 351.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(4-chlorophenyl)benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-chlorophenyl)benzoxazole (104mg, 0.30mmol) and 1,2,4-benzenetricarboxylic anhydride (58mg, 0.33mmol) the title compound was obtained (67mg, 43%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.33(m, 3H), 8.12(d, 1H), 8.05(d, 1H), 7.86(d, 1H), 7.77(d, 1H), 7.70(dd, 1H), 7.55-7.48(m, 3H), 3.89(s, 3H). MS m/z 525.1 $(M+H)^+$.

Example 19: 2-[2-Methoxy-5-[5-(3,4-dimethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

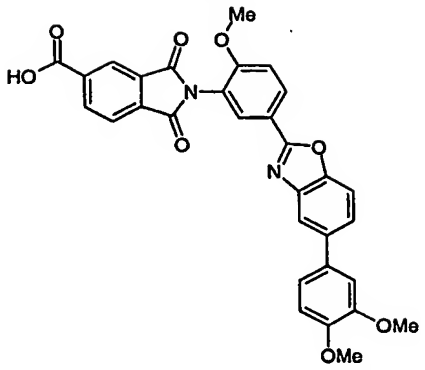
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)benzoxazole

Prepared by the method of Example 15d) from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3,4-dimethoxyphenylboronic acid (157mg, 0.85mmol) the subtitle compound was obtained (180mg, 78%). ^{1}H NMR ($CDCl_3$) δ 8.74 (d, 1H), 8.44 (dd, 1H), 7.91 (d, 1H) ,7.62 (d, 1H), 7.57 (dd, 1H), 7.25 (d, 1H), 7.19-7.14 (m, 2H), 6.98 (d, 1H), 4.07 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)benzoxazole (157mg, 0.39mmol) the subtitle compound was obtained (137mg, 93%). MS m/z 377.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(3,4-dimethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)benzoxazole (137mg, 0.36mmol) and 1,2,4-benzenetricarboxylic anhydride (69mg, 0.39mmol) the title compound was obtained (101mg, 51%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.37-8.32(m, 3h), 8.13(d, 1h), 8.02(d, 1H), 7.80(d, 1H), 7.68(dd, 1H), 7.50(d, 1H), 7.30-7.24(m, 3), 7.05(d, 1H), 3.88(s, 3H), 3.87(s, 3H), 3.80(s, 3H). MS m/z 551.2 $(M+H)^+$.

Example 20: 2-[2-Methoxy-5-[5-(2-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

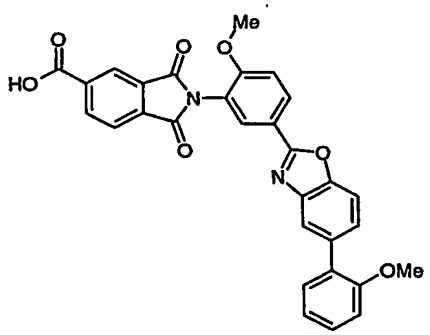
a) 2-(3-Nitro-4-methoxyphenyl)-5-(2-methoxyphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 2-methoxyphenylboronic acid (130mg, 76%) the subtitle compound was obtained (163mg, 76%). ^{1}H NMR ($CDCl_3$) δ 8.75(d, 1H), 8.45(dd, 1H), 7.93(d, 1H), 7.61(d, 1H), 7.54(dd, 1H), 7.39-7.34(m, 2H), 7.25(d, 1H), 7.09-7.01(m, 2H), 4.07(s, 3H), 3.83(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(2-methoxyphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl-5-(2-methoxyphenyl)benzoxazole (130mg, 0.35mmol) the subtitle compound was obtained (120mg, 99%). MS m/z 347.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(2-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(2-methoxyphenyl)benzoxazole (346mg, 0.40mmol) and 1,2,4-benzenetricarboxylic anhydride (77mg, 0.44mmol) the title compound was obtained (61mg, 29%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-

8.33(m, 3H), 8.13(d, 1H), 7.82(d, 1H), 7.78(d, 1H), 7.49(d, 2H), 7.36(m, 2H), 7.14(d, 1H), 7.06(t, 1H), 3.89(s, 3H), 3.79(s, 3H). MS m/z 521.2 $(M+H)^+$.

Example 21: 2-[2-Methoxy-5-[5-(3,4-dichloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

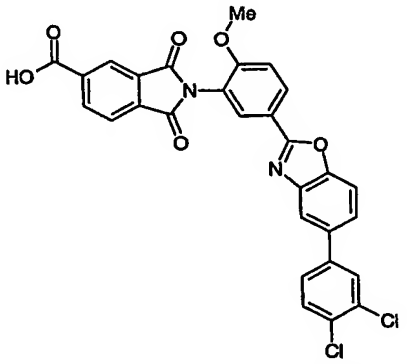
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3,4-dichlorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3,4-dichlorophenylboronic acid (176mg, 0.85mmol) the subtitle compound was obtained (176mg, 74%). ^{1}H NMR ($CDCl_3$) δ 8.74(d, 1H), 8.44(dd, 1H), 7.89(d, 1H), 7.70(d, 1H), 7.65(d, 1H), 7.54(d, 2H), 7.44(dd, 1H), 7.26(d, 1H), 4.08(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3,4-dichlorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3,4-dichlorophenyl)benzoxazole (164mg, 0.39mmol) the subtitle compound was obtained (114mg, 76%). MS m/z 385.0 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(3,4-dichloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3,4-dichlorophenyl)benzoxazole (114mg, 0.30mmol) and 1,2,4-benzenetricarboxylic anhydride (58mg, 0.33mmol) the title compound was obtained (88mg, 53%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.33(m, 3H), 8.13-8.10(m, 2H), 8.03(d, 1H), 7.76(d, 1H), 7.77-7.75(m, 3H), 7.49(d, 1H), 3.89(s, 3H). MS m/z 559.1$(M+H)^+$.

Example 22: 2-[2-Methoxy-5-[5-(3-chloro-4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

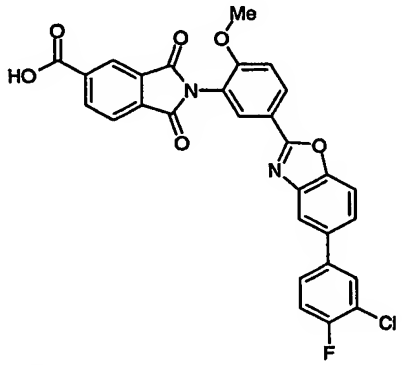
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-chloro-4-fluorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-chloro-4-fluorophenylboronic acid (150mg, 0.85mmol) the subtitle compound was obtained (163mg, 72%). ^{1}H NMR ($CDCl_3$) δ 8.74(d, 1H), 8.45(dd, 1H), 7.87(d, 1H), 7.64(m, 2H), 7.52(dd, 1H), 7.49-7.44(m, 1H), 7.28-7.21(m, 2H), 4.08(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-chloro-4-fluorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-chloro-4-fluorophenyl)benzoxazole (150mg, 0.38mmol) the subtitle compound was obtained (107mg, 76%). MS m/z 369.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(3-chloro-4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-fluoro-3-chlorophenyl)benzoxazole (107mg, 0.29mmol) and 1,2,4-benzenetricarboxylic anhydride (56mg, 0.31mmol) the title compound was obtained (101mg, 64%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.33(m, 3H), 8.12(d, 1H), 8.09(d, 1H), 7.98(dd, 1H), 7.85(d, 1H), 7.79-7.71(m, 2H), 7.55(d, 1H), 7.49(d, 1H). MS m/z 543.1 $(M+H)^+$.

Example 23: 2-[2-Methoxy-5-[5-(4-trifluoromethyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

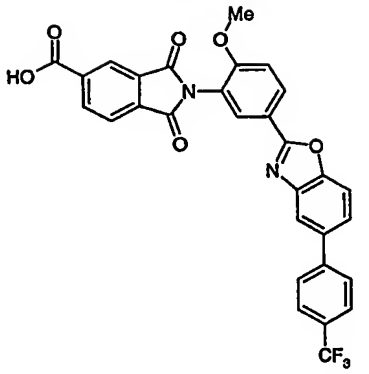
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-trifluoromethylphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-trifluoromethylphenylboronic acid (161mg, 0.85mmol) the subtitle compound was obtained (204mg, 58%). ^{1}H NMR (DMSO) δ 8.64(d, 1H), 8.46(dd, 1H), 8.16(d, 1H), 7.97(d, 2H), 7.92(d, 1H), 7.85-7.78(m, 3H), 7.63(d, 1H), 4.05(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-trifluoromethylphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-trifluoromethylphenyl)benzoxazole (113mg, 0.27mmol) the subtitle compound was obtained (107mg, 99%). MS m/z 415.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(4-trifluoromethyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-trifluorophenyl)benzoxazole (107mg, 0.28mmol) and 1,2,4-benzenetricarboxylic anhydride (53mg, 0.30mmol) the title compound was obtained (107mg, 69%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.34(m, 3H), 8.14-8.10(m, 2H), 7.98(d, 2H), 7.89(d, 1H), 7.84(d, 2H), 7.77(dd, 1H), 7.50(d, 1H), 3.89(s, 3H). MS m/z 559.1 $(M+H)^+$.

Example 24: 2-[2-Methoxy-5-[5-[4-(1-hydroxyethyl)]phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

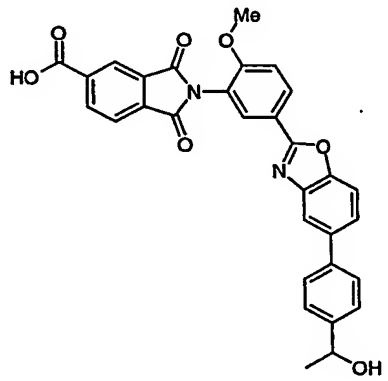
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-acetylphenyl)benzoxazole

Prepared by the method of Example 15d) from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-acetylphenylboronic acid (139mg, 0.85mmol) the subtitle compound was obtained (119mg, 36%). ^{1}H NMR (DMSO) δ 8.64(d, 1H), 8.46(dd, 1H), 8.16(d, 1H), 8.06(d, 2H), 7.93-7.90(m, 3H), 7.81(dd, 1H), 7.63(d, 1H), 4.05(s, 3H), 2.63(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-[ethyl-2-hydroxy]phenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-acetylphenyl)benzoxazole (51mg, 0.13mmol) the subtitle compound was obtained (43mg, 99%). MS m/z 389.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-[4-(1-hydroxyethyl)]phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl-5-(4-[ethyl-2-hydroxy]phenyl)benzoxazole (43mg, 0.12mmol) and 1,2,4-benzenetricarboxylic anhydride (25mg,

0.13mmol) the title compound was obtained (6mg, 9%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.33(m, 3H), 8.12(d, 1H), 8.02(d, 1H), 7.84(D, 1H), 7.74-7.67(m, 3H), 7.49(m, 3H), 5.84(q, 1H), 3.89(s, 3H), 1.51(d, 3H). MS m/z 517.1 $(M+H)^+$.

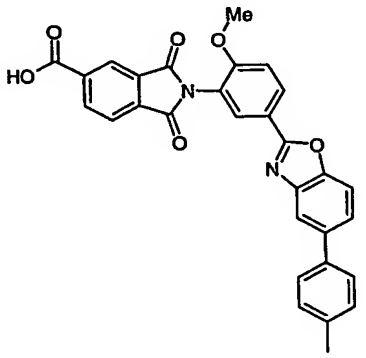
Example 25: 2-[2-Methoxy-5-[5-(4-methyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-methylphenylboronic acid (116 mg, 0.85mmol) the subtitle compound was obtained (201mg, 66%). ^{1}H NMR (DMSO) δ 8.68(d, 1H), 8.51(dd, 1H), 8.07(d, 1H), 7.90(d, 1H), 7.74-7.67(m, 3H), 7.36-7.33(d, 2H), 4.10(s, 3H), 2.41(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-methylphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(4-methylphenyl)benzoxazole (82mg, 0.23mmol) the subtitle compound was obtained (59mg, 99%). MS m/z 361.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(4-methyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl-5-(4-methylphenyl)benzoxazole (59mg, 0.18mmol) and 1,2,4-benzenetricarboxylic anhydride (38mg, 0.20mmol) the title compound was obtained (69mg, 50%). ^{1}H NMR (DMSO) δ 8.45(d, 1H), 8.38-8.32(m, 3H), 8.12(d, 1H), 7.99(d, 1H), 7.82(d, 1H), 7.69-7.61(m, 3H), 7.49(d, 1H), 7.29(d, 2H), 3.89(s, 3H), 2.36(s, 3H). MS m/z 505.1 $(M+H)^+$.

Example 26: 2-[2-Methoxy-5-[5-[(5-methyl)thiophen-2yl]benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

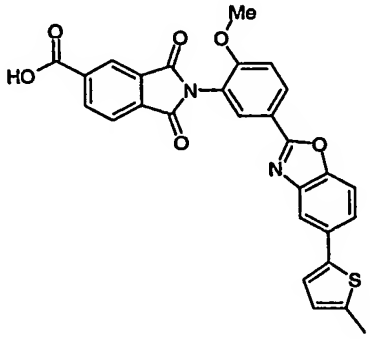
a) 2-(3-Nitro-4-methoxyphenyl)-5-[(5-methyl)thiophen-2yl]benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 2-(5-methyl)thiopheneboronic acid (121mg, 0.85mmol) the subtitle compound was obtained (301mg, 96%). ^{1}H NMR (DMSO) δ 8.62(d, 1H), 8.43(dd, 1H), 7.97(d, 1H), 7.80(d, 1H), 7.63(m, 2H), 7.38(d, 1H), 6.84(dd, 1H), 4.05(s, 3H), 2.50(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-[(5-methyl)thiophen-2yl]benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-[(5-methyl)thiophen-2yl]benzoxazole (75mg, 0.20mmol) the subtitle compound was obtained (64mg, 99%). MS m/z 367.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-[(5-methyl)thiophen-2yl]benzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl-5-[(5-methyl)thiophen-2-yl]benzoxazole (64mg, 0.19mmol) and 1,2,4-benzenetricarboxylic anhydride (40mg, 0.20mmol) the title compound was obtained (62mg, 64%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.36-8.30(m, 3H), 8.11(d, 1H), 7.94(d, 1H), 7.77(d, 1H), 7.61(dd, 1H), 7.49(d, 1H), 7.36(d, 1H), 6.84(dd, 1H), 3.89(s, 3H), 2.50(s, 3H). MS m/z 511.1 $(M+H)^+$.

Example 27: 2-[2-Methoxy-5-[5-(4-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

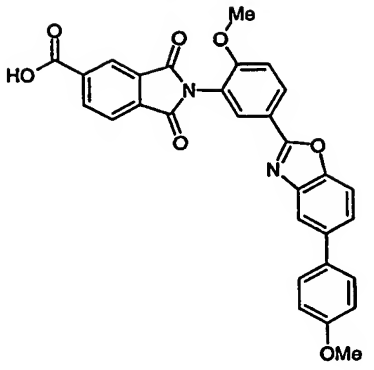
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-methoxyphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-methoxyphenylboronic acid (129mg, 0.85mmol) the subtitle compound was obtained (193mg, 60%). ^{1}H NMR (DMSO) δ 8.63(d, 1H), 8.45(dd, 1H), 7.99(d, 1H), 7.83(d, 1H), 7.67(d, 3H), 7.62(d, 1H), 7.05(d, 2H), 4.05(s ,3H), 3.81(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-methoxyphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(4-methoxyphenyl)benzoxazole (102mg, 0.27mmol) the subtitle compound was obtained (103mg, 99%). MS m/z 377.1 $(M+H)^+$.

c) 2-[2-Methoxy-5-[5-(4-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-methoxyphenyl)benzoxazole (103mg, 0.30mmol) and 1,2,4-benzenetricarboxylic anhydride (63mg, 0.20mmol) the title compound was obtained (91mg, 58%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38-8.32(m, 3H), 8.12(d, 1H), 7.96(d, 1H), 7.80(d, 1H), 7.69-7.63(m, 3H), 7.49(d, 1H), 7.05(d, 2H), 3.89(s, 3H), 3.81(s, 3H). MS m/z 521.1 $(M+H)^+$.

Example 28: 2-[2-Methoxy-5-[5-(3-cyano)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

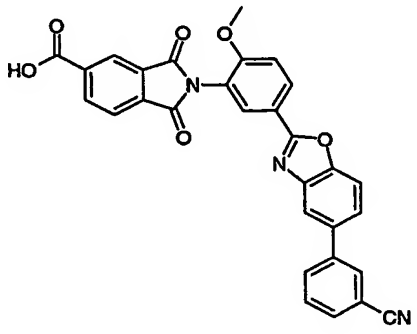
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-cyanophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-cyanophenylboronic acid (126mg, 0.86mmol) the subtitle compound was obtained (65mg, 31%). ^{1}H NMR (DMSO) δ 8.75(d, 1H), 8.57(dd, 1H), 8.35(t, 1H), 8.29(d, 1H), 8.21(dt, 1H), 8.00(d, 1H), 7.97(dt, 1H), 7.93(d, 1H), 7.80(t, 1H), 7.74(d, 1H), 4.17(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-cyanophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-cyanophenyl)benzoxazole (50mg, 0.14mmol) the subtitle compound was obtained (33mg, 71%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3-cyano)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-cyanophenyl)benzoxazole (31mg, 0.09mmol) and 1,2,4-benzenetricarboxylic anhydride (17mg, 0.09mmol) the title compound was obtained, (14mg, 30%). ^{1}H NMR (DMSO) δ 8.47(dd, 1H), 8.38(d, 1H), 8.35(q, 2H), 8.25(t, 1H), 8.17(d, 1H), 8.13(d, 1H), 8.11(dt, 1H), 7.90(d, 1H), 7.85(d, 1H), 7.80(dd, 1H), 7.70(t, 1H), 7.50(d, 1H), 3.90(s, 3H). MS: 516m/z $(M+H)^+$.

Example 29: 2-[2-Methoxy-5-[5-(3-methyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

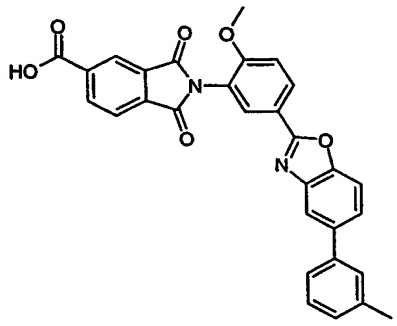
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-methylphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-methylphenylboronic acid (117mg, 0.86mmol) the subtitle compound was obtained, (69mg, 33%). ^{1}H NMR (DMSO) δ 8.64(d, 1H), 8.47(dd, 1H), 8.14(d, 1H), 7.86(d, 1H), 7.72(dd, 1H), 7.64(d, 1H), 7.55(m, 2H), 7.39(t, 1H), 7.22(d, 1H), 4.07(s, 1H), 2.40(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-methylphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-methylphenyl)benzoxazole (61mg, 0.17mmol) the subtitle compound was obtained, (47mg, 84%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3-methyl)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-methylphenyl)benzoxazole (44mg, 0.13mmol) and 1,2,4-benzenetricarboxylic anhydride (25mg, 0.13mmol) the title compound was obtained, (31mg, 46%). ^{1}H NMR (DMSO) δ 8.46(dd, 1H), 8.38(d, 1H), 8.34(q, 2H), 8.13(d, 1H), 8.02(d, 1H), 7.84(d, 1H), 7.68(dd, 1H), 7.52(m, 3H), 7.48(t, 1H), 7.20(d, 1H), 3.89(s, 3H), 2.40(s, 3H). MS: 505m/z $(M+H)^+$.

Example 30: 2-[2-Methoxy-5-[5-(3-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-methoxyphenyl)benzoxazole

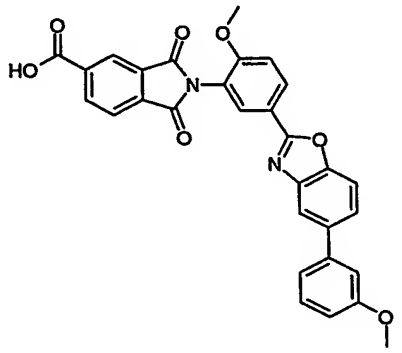
Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-methoxyphenylboronic acid (131mg, 0.86mmol) the subtitle compound was

obtained, (98mg, 45%). ^{1}H NMR (DMSO) δ 8.71(d, 1H), 8.52(dd, 1H), 8.35(t, 1H), 8.17(d, 1H), 7.93(d, 1H), 7.82(dd, 1H), 7.69(d, 1H), 7.48(t, 1H), 7.36(m, 2H), 7.03(dd, 1H), 4.12(s, 3H), 3.90(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-methoxyphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-methoxyphenyl)benzoxazole (87mg, 0.23mmol) the subtitle compound was obtained, (66mg, 82%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3-methoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-methoxyphenyl)benzoxazole (62mg, 0.18mmol) and 1,2,4-benzenetricarboxylic anhydride (35mg, 0.18mmol) the title compound was obtained, (47mg, 50%). ^{1}H NMR (DMSO) δ 8.35(dd, 1H), 8.28(d, 1H), 8.22(q, 2H), 8.02(d, 1H), 7.93(d, 1H), 7.72(d, 1H), 7.60(dd, 1H), 7.40(d, 1H), 7.30(t, 1H), 7.17(m, 2H), 6.85(dd, 1H), 3.79(s, 3H), 3.75(s, 3H). MS: 521m/z $(M+H)^+$.

Example 31: 2-[2-Methoxy-5-[5-(3-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

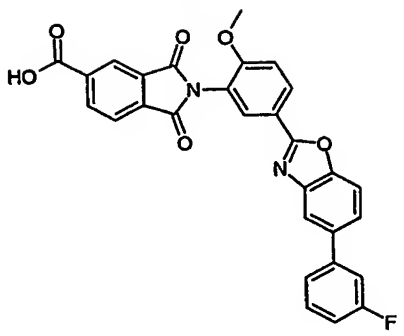
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-fluorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-fluorophenylboronic acid (120mg, 0.86mmol) the subtitle compound was obtained, (103mg, 49%). ^{1}H NMR (DMSO) δ 8.59(d, 1H), 8.40(dd, 1H), 8.08(d, 1H), 7.82(d, 1H), 7.72(dd, 1H), 7.52(m, 4H), 7.17(dt, 1H), 4.02(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-fluorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-fluorophenyl)benzoxazole (94mg, 0.26mmol) the subtitle compound was obtained, (73mg, 85%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-fluorophenyl)benzoxazole (67mg, 0.20mmol) and 1,2,4-benzenetricarboxylic anhydride (38mg, 0.20mmol) the title compound was obtained, (65mg, 64%). ^{1}H NMR (DMSO) δ 8.33(dd, 1H), 8.28(d, 1H), 8.22(q, 2H), 8.02(d, 1H), 7.98(d, 1H), 7.74(d, 1H), 7.64(dd, 1H), 7.45(m, 3H), 7.38(d, 1H), 7.10(dt, 1H), 3.77(s, 3H). MS: 509 m/z $(M+H)^+$.

Example 32: 2-[2-Methoxy-5-[5-(3-chloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

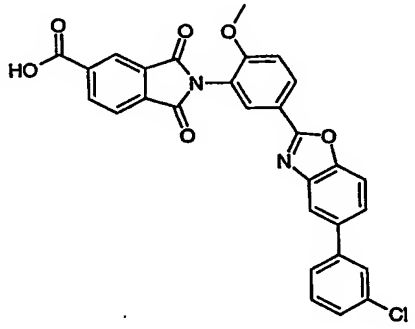
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-chlorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-chlorophenylboronic acid (134mg, 0.86mmol) the subtitle compound was obtained, (72mg, 33%). ^{1}H NMR (DMSO) δ 8.71(d, 1H), 8.53(dd, 1H), 8.19(d, 1H), 7.95(d, 1H), 7.88(t, 1H), 7.83(dd, 1H), 7.79(d, 1H), 7.70(d, 1H), 7.58(t, 1H), 7.52(d, 1H), 4.12(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-chlorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-chlorophenyl)benzoxazole (62mg, 0.16mmol) the subtitle compound was obtained, (44mg, 77%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3-chloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-chlorophenyl)benzoxazole (42mg, 0.12mmol) and 1,2,4-benzenetricarboxylic anhydride (23mg, 0.12mmol) the title compound was obtained, (33mg, 53%). ^{1}H NMR (DMSO) δ 8.48(dd, 1H), 8.42(d,

1H), 8.37(q, 2H), 8.16(d, 1H), 8.13(d, 1H), 7.89(d, 1H), 7.84(t, 1H), 7.75(m, 2H), 7.52(m, 3H), 3.91(s, 3H). MS: 525 m/z $(M+H)^+$.

Example 33: 2-[2-Methoxy-5-[5-(4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

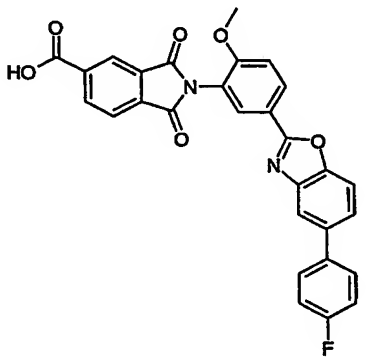
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-fluorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-fluorophenylboronic acid (120mg, 0.86mmol) the subtitle compound was obtained, (135mg, 65%). ^{1}H NMR (DMSO) δ 8.64(d, 1H), 8.45(dd, 1H), 8.05(d, 1H), 7.87(d, 2H), 7.78(dd, 1H), 7.72(dd, 1H), 7.62(d, 2H), 7.33(t, 1H), 4.08(s, 3H).

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-fluorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(4-fluorophenyl)benzoxazole (122mg, 0.33mmol) the subtitle compound was obtained, (66mg, 59%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(4-fluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-fluorophenyl)benzoxazole (55mg, 0.16mmol) and 1,2,4-benzenetricarboxylic anhydride (31mg, 0.16mmol) the title compound was obtained, (41mg, 49%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38(d, 1H), 8.34(q, 2H), 8.12(d, 1H), 8.02(d, 1H), 7.84(d, 2H), 7.78(dd, 1H), 7.68(dd, 1H), 7.49(d, 2H), 7.32(t, 1H), 3.88(s, 3H). MS: 509 m/z $(M+H)^+$.

Example 34: 2-[2-Methoxy-5-[5-(2,4-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

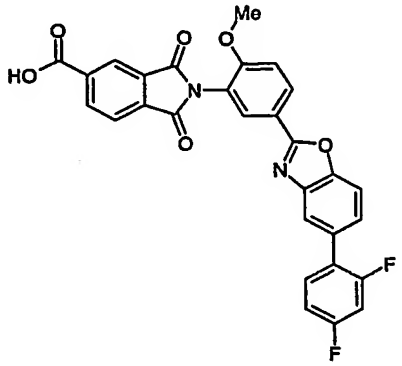
a) 2-(3-Nitro-4-methoxyphenyl)-5-(2,4-difluorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 2,4-difluorophenylboronic acid (136mg, 0.86mmol) the subtitle compound was obtained, (57mg, 26%). ^{1}H NMR (DMSO) δ 8.71(d, 1H), 8.53(dd, 1H), 8.01(s, 1H), 7.97(d, 1H), 7.70(m, 3H), 7.48(dt, 1H), 7.30(dt, 1H), 4.12(s, 3H). MS: 383m/z $(M+H)^+$.

b) 2-(3-Amino-4-methoxyphenyl)-5-(2,4-difluorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(2,4-difluorophenyl)benzoxazole (50mg, 0.15mmol) the subtitle compound was obtained, (50mg, 95%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(2,4-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(2,4-difluorophenyl)benzoxazole (50mg, 0.14mmol) and 1,2,4-benzenetricarboxylic anhydride (27mg, 0.16mmol) the title compound was obtained, (25mg, 33%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38(d, 1H), 8.35(q, 2H), 8.12(d, 1H), 7.91(s, 1H), 7.87(d, 1H), 7.67(dt, 1H), 7.57(dt, 1H), 7.50(d, 1H), 7.41(m, 1H), 7.23(dt, 1H), 3.89(s, 3H). MS: 527m/z $(M+H)^+$.

Example 35: 2-[2-Methoxy-5-[5-(3,5-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

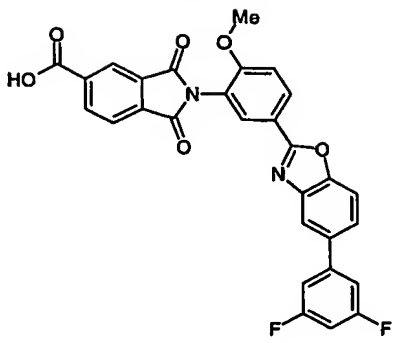
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3,5-difluorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3,5-difluorophenylboronic acid (136mg, 0.86mmol) the subtitle compound was obtained, (120mg, 64%). ^{1}H NMR (DMSO) δ 8.70(d, 1H), 8.52(dd, 1H), 8.26(d, 1H), 7.96(d, 1H), 7.88(dd, 1H), 7.69(d, 1H), 7.61(dd, 2H), 7.33(tt, 1H), 4.12(s, 3H). MS: 383m/z $(M+H)^+$.

b) 2-(3-Amino-4-methoxyphenyl)-5-(3,5-difluorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3,5-difluorophenyl)benzoxazole (120mg, 0.31mmol) the subtitle compound was obtained, (90mg, 82%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(3,5-difluoro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3,5-difluorophenyl) benzoxazole (90mg, 0.26mmol) and 1,2,4-benzenetricarboxylic anhydride (49mg, 0.28mmol) the title compound was obtained, (58mg, 43%). ^{1}H NMR (DMSO) δ 8.60(dd, 1H), 8.52(d, 1H), 8.49(d, 2H), 8.31(d, 1H), 8.26(d, 1H), 8.01(d, 1H), 7.93(dd, 1H), 7.69(dd, 2H), 7.64(d, 1H), 7.40(tt, 1H), 4.04(s, 3H). MS: 527m/z $(M+H)^+$.

Example 36: 2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

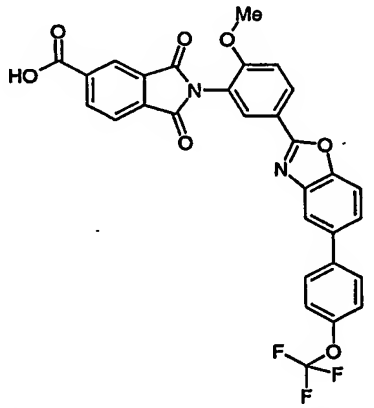
a) 2-(3-Nitro-4-methoxyphenyl)-5-(4-trifluoromethoxyphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 4-trifluoromethoxyphenylboronic acid (177mg, 0.86mmol) the subtitle compound was obtained, (119mg, 48%). ^{1}H NMR (DMSO) δ 8.70(s, 1H), 8.52(d, 1H), 8.16(s, 1H), 7.93(d, 3H), 7.81(d, 2H), 7.68(d, 1H), 7.55(d, 1H), 4.12(s, 3H). MS: 431m/z $(M+H)^+$.

b) 2-(3-Amino-4-methoxyphenyl)-5-(4-trifluoromethoxyphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(4-trifluoromethoxy phenyl)benzoxazole (127mg, 0.30mmol) the subtitle compound was obtained, (90mg, 76%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(4-trifluoromethoxyphenyl)benzoxazole (90mg, 0.23mmol) and 1,2,4-benzenetricarboxylic anhydride

(43mg, 0.25mmol) the title compound was obtained, (52mg, 40%). ^{1}H NMR (DMSO) δ 8.32(dd, 1H), 8.25(d, 1H), 8.22(q, 2H), 7.99(d, 1H), 7.95(d, 1H), 7.76(s, 1H), 7.73(s, 2H), 7.59(dd, 1H), 7.36(dd, 3H), 3.77(s, 3H). MS: 575m/z $(M+H)^+$.

Example 37: 2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

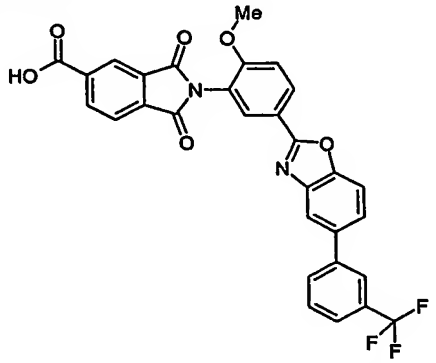
a) 2-(3-Nitro-4-methoxyphenyl)-5-(3-trifluoromethylphenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 3-trifluoromethylphenylboronic acid (163mg, 0.86mmol) the subtitle compound was obtained, (120mg, 51%). ^{1}H NMR (DMSO) δ 8.70(s, 1H), 8.52(d, 1H), 8.24(s, 1H), 8.11(s, 1H), 7.97(d, 1H), 7.86(d, 1H), 7.81(s, 2H), 7.68(d, 1H), 4.11(s, 3H). MS: 415m/z $(M+H)^+$.

b) 2-(3-Amino-4-methoxyphenyl)-5-(3-trifluoromethylphenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(3-trifluoromethyl phenyl) benzoxazole (120mg, 0.29mmol) the subtitle compound was obtained, (110mg, 99%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(4-trifluoromethoxy)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(3-trifluoromethylphenyl)benzoxazole (110mg, 0.29mmol) and 1,2,4-benzenetricarboxylic anhydride (55mg, 0.31mmol) the title compound was obtained, (78mg, 49%). ^{1}H NMR (DMSO) δ 8.45(dd, 1H), 8.38(d, 1H), 8.34(q, 2H), 8.15(d, 1H), 8.12(d, 1H), 8.05(s, 2H), 7.88(d, 1H), 7.78(dd, 1H), 7.75(s, 2H), 7.50(d, 1H), 3.89(s, 3H). MS: 575m/z $(M+H)^+$.

Example 38: 2-[2-Methoxy-5-[5-(2,4-dichloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

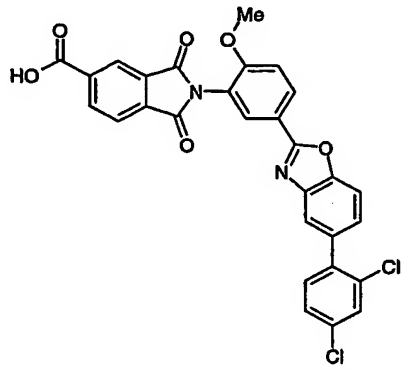
a) 2-(3-Nitro-4-methoxyphenyl)-5-(2,4-dichlorophenyl)benzoxazole

Prepared by the method of Example 15d), from 2-(3-nitro-4-methoxyphenyl)-5-bromobenzoxazole (200mg, 0.57mmol) and 2,4-dichlorophenylboronic acid (164mg, 0.86mmol) the subtitle compound was obtained, (148mg, 62%). ^{1}H NMR (DMSO) δ 8.69(s, 1H), 8.51(d, 1H), 7.93(d, 1H), 7.84(s, 1H), 7.60(m, 3H), 4.12(s, 3H). MS: 415m/z $(M+H)^+$.

b) 2-(3-Amino-4-methoxyphenyl)-5-(2,4-dichlorophenyl)benzoxazole

Prepared by the method of Example 15e), from 2-(3-nitro-4-methoxyphenyl)-5-(2,4-dichlorophenyl)benzoxazole (148mg, 0.36mmol) the subtitle compound was obtained, (110mg, 80%). The product was used directly in the next step without purification.

c) 2-[2-Methoxy-5-[5-(2,4-dichloro)phenylbenzoxazol-2-yl]phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-methoxyphenyl)-5-(2,4-dichlorophenyl)benzoxazole (110mg, 0.29mmol) and 1,2,4-benzenetricarboxylic anhydride (55mg, 0.31mmol) the title compound was obtained, (62mg, 39%). ^{1}H NMR (DMSO) δ 8.36(dd, 1H), 8.29(d, 1H), 8.26(q, 2H), 8.03(d, 1H), 7.77(d, 1H), 7.74(d, 1H), 7.69(s, 1H), 7.45(s, 2H), 7.41(d, 1H), 7.36(dd, 1H), 3.80(s, 3H). MS: 575m/z $(M+H)^+$.

Example 39: 2-[2-Propargyloxy-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

(a) 2-(3-Nitro-4-propargyloxy)-5-phenylbenzoxazole

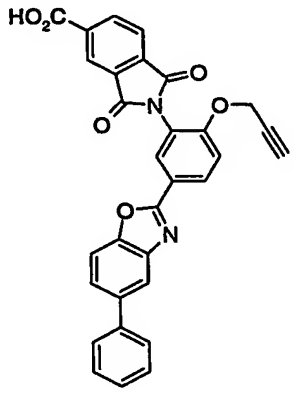
Potassium carbonate (330 mg, 2.4 mmol) was added in one portion to a stirred solution of 2-(3-nitro-4-fluoro)-5-phenylbenzoxazole (400mg, 1.2 mmol) and propargyl alcohol (0.07 ml, 1.2 mmol) in DMF (4 ml) at room temperature under argon. The resulting mixture was heated at 85 °C for 16h. After being allowed to cool to room temperature the mixture was poured into water (5 ml) and 10% aqueous hydrochloric acid was added until pH 3. Then, the aqueous mixture was extracted with EtOAc (3 × 5 ml) and the combined organic extracts were washed with 10% aqueous hydrochloric acid (10 ml), brine (5 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the subtitle compound (408 mg, 92%) as a brown solid which was sufficiently pure (by TLC and ^{1}H NMR spectroscopy) to be used in the next step, R_F(3:1 Petrol-EtOAc) 0.41; ^{1}H NMR (DMSO) δ 8.69(1H, d, J= 2.5Hz, Ar), 8.52(1H, dd, J= 2.5Hz and 9.0, Ar), 8.10(1H, d, J= 1.5Hz, Ar), 7.92(1H, d, J= 8.5Hz, Ar), 7.79-7.69(4H, m, Ar), 7.54(2H, t, J= 7.0Hz, Ar), 7.43(1H, t, J= 7.0Hz, Ar), 5.21(2H, d, J= 2.5Hz, CH_2), 3.85(1H, t, J= 2.5Hz, CH).

(b) 2-(3-Amino-4-propargyloxy)-5-phenylbenzoxazole

Tin(II) chloride dihydrate (148 mg, 0.7 mmol) was added in one portion to a stirred suspension of 2-(3-nitro-4-propargyloxy)-5-phenylbenzoxazole (100 mg, 0.3 mmol), powdered zinc (43 mg, 0.7 mmol) and 37% aqueous hydrochloric acid (0.2 ml, 4.9 mmol) in AcOH (1.5 ml) at room temperature. After 2h, 6 M aqueous sodium hydroxide solution was added until pH 10 was obtained and the mixture was extracted with EtOAc (3 × 3 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude subtitle compound (62 mg, 67%) as a pale yellow solid which was sufficiently pure (by TLC and ^{1}H NMR

spectroscopy) to be used in the next step, R_F(3:1 Petrol-EtOAc) 0.36; ^{1}H NMR ($CDCl_3$) δ 7.84(1H, d, J= 1.0Hz, Ar), 7.60-7.52(4H, m, Ar), 7.49-7.44(2H, m, Ar), 7.39(2H, brt, J= 7.0Hz, Ar), 7.28 [1H, tt (appearing as a t), J= 7.5Hz, Ar], 6.93(1H, d, J= 8.0Hz, Ar), 4.73(2H, d, J= 2.5Hz, CH_2), 3.93(2H, br s, NH_2), 2.49(1H, t, J= 2.5Hz, CH).

(c) 2-[2-Propargyloxy-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-propargyloxy)-5-phenylbenzoxazole (62 mg, 0.2 mmol) and 1,2,4-benzene tricarboxylic anhydride (35 mg, 0.2 mmol) in AcOH (1 ml) gave the title compound (27 mg, 29%) as a brown solid, ^{1}H NMR (DMSO) δ 13.87(1H, br s, CO_2H), 8.52-8.40(4H, m, Ar), 8.18(1H, d, J= 8.0Hz, Ar), 8.10(1H, d, J= 1.5Hz, Ar), 7.91(1H, d, J= 8.5Hz, Ar), 7.81-7.74(3H, m, Ar), 7.62-7.52(3H, m, Ar), 7.44(1H, br t, J= 7.0Hz, Ar), 5.04(2H, d, J= 2.0Hz, CH_2), 3.72(1H, t, J= 2.0Hz, CH).

Example 40: 2-[2-Ethoxy-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

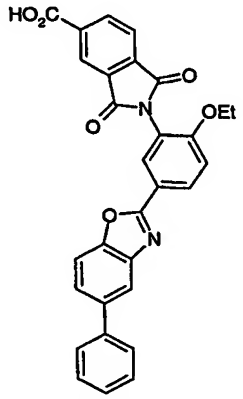
(a) 2-(3-Nitro-4-ethoxyphenyl)-5-phenylbenzoxazole

Sodium ethoxide (41 mg, 0.6 mmol) was added portionwise to a stirred suspension of 2-(3-nitro-4-fluoro)-5-phenylbenzoxazole (200 mg, 0.6 mmol) in EtOH (2 ml) at 0 °C under argon. When gas evolution had visibly ceased the mixture was allowed to warm to room temperature and then heated at 85 °C for 1h. After being allowed to cool to room temperature the mixture was carefully diluted with water (5 ml) and extracted with EtOAc (3 × 5 ml). The combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude subtitle compound (207 mg, 96%) as a pale brown solid which was sufficiently pure (by TLC and ^{1}H NMR spectroscopy) to be used in the next step, R_F(3:1 Petrol-EtOAc) 0.37; ^{1}H NMR (DMSO) δ 8.65(1H, d, J= 2.0Hz, Ar), 8.45(1H, dd, J= 2.5Hz and 9.0, Ar), 8.08(1H, d, J= 1.5Hz, Ar), 7.90(1H, d, J= 8.5Hz, Ar), 7.79-7.74(3H, m, Ar), 7.63(1 H, d, J= 9.0Hz, Ar), 7.54(2 H, t, J= 7.0Hz, Ar), 7.43(1 H, t, J= 7.0Hz, Ar), 4.38(2 H, q, J= 7.0Hz, CH_2), 1.43(1H, t, J= 7.0Hz, CH_3).

(b) 2-(3-Amino-4-ethoxyphenyl)-5-phenylbenzoxazole

Prepared by the method of Example 15e), from palladium (10 mol%) on carbon (10 mg, 0.1 mmol) and 2-(3-nitro-4-ethoxyphenyl)-5-phenylbenzoxazole (100 mg, 0.3 mmol) in dioxane (1 ml) which gave the crude subtitle compound (51 mg, 56%) as a white solid which was sufficiently pure (by TLC and ^{1}H NMR spectroscopy) to be used in the next step, R_F(2:1 Petrol-EtOAc) 0.50; ^{1}H NMR ($CDCl_3$) δ 7.92(1H, d, *J* 1.0, Ar), 7.68-7.60(4H, m, Ar), 7.57-7.51(2H, m, Ar), 7.47(2H, br t, J= 7.0Hz, Ar), 7.36(1H, tt, J= 1.0Hz and 6.5, Ar), 6.89(1H, d, J= 8.5Hz, Ar), 4.16(2H, q, J= 7.0Hz, CH_2), 3.98(2H, br s, NH_2), 1.49(1H, t, J= 2.5Hz, CH_3).

(c) 2-[2-Ethoxy-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f), from 2-(3-amino-4-ethoxy)-5-phenylbenzoxazole (43 mg, 0.1 mmol) and 1,2,4-benzene tricarboxylic anhydride (25 mg, 0.1 mmol) in AcOH (1 ml) gave the title compound (27 mg, 41%) as a white solid, ^{1}H NMR δ (DMSO) 13.88(1H, br s, CO_2H), 8.49(1H, d, J= 8.0Hz, Ar), 8.40-8.36(3H, m, Ar), 8.07(1H, s, Ar), 7.90(1H, d, J= 8.5Hz, Ar), 7.79-7.72(3H, m, Ar), 7.54(3H, br t, J= 7.0Hz, Ar), 7.45-7.40(1H, m, Ar), 4.25(2H, q, J= 6.5Hz, CH_2), 1.26(3H, t, J= 6.5Hz, CH_3).

Example 41: 2-[2-(2-Methoxyethylamino)-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

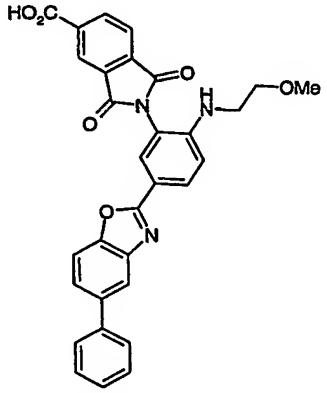
(a) 2-[3-Nitro-4-(2-methoxy ethyl amino)]-5-phenylbenzoxazole

2-Methoxy ethylamine (2.0 ml, 23.9 mmol) was added dropwise to 2-(3-nitro-4-fluoro)-5-phenylbenzoxazole (200 mg, 0.6 mmol) with stirring at room temperature under argon. The resulting suspension was stirred at room temperature for 15min. EtOAc (10ml) was then added and the mixture was washed with 10% aqueous hydrochloric acid (10ml), brine (10ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude subtitle compound (235 mg, 100%) as an orange solid which was sufficiently pure (by TLC and ^{1}H NMR spectroscopy) to be used in the next step, R_F(2:1 Petrol-EtOAc) 0.18; ^{1}H NMR ($CDCl_3$) δ 9.01(1H, d, J= 2.5Hz, Ar), 8.49(1H, br t, J= ~4.5Hz, NH), 8.24(1H, dd, J= 2.0 and 9.0Hz, Ar), 7.85(1H, d, J= 1.0Hz, Ar), 7.58-7.48(4H, m, Ar), 7.43-7.38(2H, m, Ar), 7.32-7.27(1H, m, Ar), 6.95(1H, d, J= 9.0Hz, Ar), 3.65(2H, t, J= 5.5Hz, CH_2O), 3.52 [2H, td (appearing as a q), J= 5.5Hz, CH_2N], 3.39(3H, s, OMe).

(b) 2-[3-Amino-4-(2-methoxy ethyl amino)]-5-phenylbenzoxazole

Prepared by the method of Example 15e) from palladium (10 mol%) on carbon (10 mg, 0.1 mmol) and 2-[3-nitro-4-(2-methoxy ethyl amino)]-5-phenylbenzoxazole (100 mg, 0.3 mmol) in dioxane (1 ml) which gave the crude subtitle compound (75 mg, 81%) as a white solid which was sufficiently pure (by TLC and ^{1}H NMR spectroscopy) to be used in the next step, ^{1}H NMR ($CDCl_3$) δ 7.89(1H, d, J= 1.0Hz, Ar), 7.77(1H, dd, J= 2.0 and 8.5Hz, Ar), 7.65-7.62(3H, m, Ar), 7.58-7.51(2H, m, Ar), 7.46(2H, br t, J= 7.0Hz, Ar), 7.36(1H, br t, J= 7.0Hz, Ar), 7.36 [1H, tt (appearing as a br t), J= 7.0Hz, Ar], 6.73(1H, d, J= 8.5Hz, Ar), 3.70(2H, t, J= 5.5Hz, CH_2O), 3.43(3H, s, OMe), 3.39(2H, t, J= 5.5Hz, CH_2N).

(c) 2-[2-(2-Methoxyethylamino)-5-(5-phenylbenzoxazol-2-yl)phenyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid



Prepared by the method of Example 15f) from 2-[3-amino-4-(2-methoxy ethyl amino)]-5-phenylbenzoxazole (54 mg, 0.2 mmol) and 1,2,4-benzene tricarboxylic anhydride (29 mg, 0.2 mmol) in AcOH (1 ml) gave the title compound (10 mg, 12%) as a pale brown solid, ^{1}H NMR (DMSO) δ 13.40 (1H, br s, CO_2H), 8.52 (1H, s, Ar), 8.29-8.20 (4H, m, Ar), 8.11 (1H, s, Ar), 7.98-7.91 (2H, m, Ar), 7.81-7.74 (3H, m, Ar), 7.55 (2H, br t, J= 7.0Hz, Ar), 7.44 (1H, br t, J= 7.5Hz, Ar), 4.31-4.24 (2H, m, CH_2O), 3.61 (2H, t, J= 5.0Hz, CH_2N), 3.11 (3H, s, OMe).

Biological Data

Heparanase assay: The assay is based upon the use of the specific binding of basic fibroblast growth factor (bFGF) to heparan sulphate. Heparan sulphate can be detected via binding of bFGF using a horse radish peroxidase-conjugated bFGF antibody. Following cleavage of high molecular weight heparan sulphate by heparanase, the smaller material generated will not longer adhere to the surface of a 96 well plate and hence heparanase activity can be followed as a reduction in bFGF binding.

Nunc Maxisorp 96-well plates are coated for 16h at RT with 100μl/well 0.04mg/ml heparan sulphate in PBS. The wells are then aspirated and blocked for 1h with 200μl/well 1% BSA-PBS. Following five washes with 0.01% BSA, 0.05% Tween20 PBS (wash buffer), 100μl of recombinant human basic FGF (90ng/ml in 0.1% BSA/PBS) is added per well and the plate is incubated at room temperature for 1h.

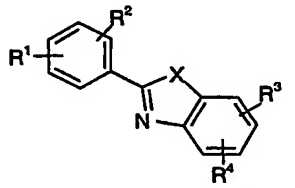
After a further five washes with the wash buffer, 10μl of test compound (in 10% DMSO) and 90μl of human heparanase in 100mM Sodium acetate, 5mM $CaCl_2$, pH 5.5 are added to each well and the plate incubated for 2h at 37°C. The wells are washed again with wash buffer and 100μl of bFGF antibody-

horse radish peroxidase conjugate added. The plate is incubated at room temperature for 1h and washed again fives with wash buffer. 100μl of TMB peroxidase substrate is added and the colour allowed to develop for 10 min. The reaction is stopped with 50μl 1M H_2SO_4 and the colour read at 450nm on a plate reader.

Compound	Inhibition of Heparanase (IC_{50},μM)
Example 1	5.0
Example 2	0.7
Example 9	3.0
Example 15	0.5
Example 27	0.4

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

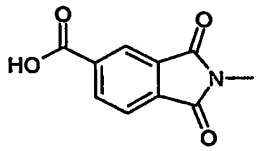


(I)

wherein

X is O or S;

R^1 is a phthalimide carboxylic acid group of formula (II):



(II)

R^2 is hydrogen, halogen, C_1-C_6 alkyl, OR^5 or NR^5R^5 wherein the R^5 substituents together with the nitrogen to which they are attached may form a 5- or 6-membered ring which may contain an additional heteroatom selected from oxygen, nitrogen and sulfur;

R^3 and R^4 are independently hydrogen, halogen, C_1-C_6 alkyl optionally substituted by hydroxy or C_1-C_3 alkoxy, CF_3, OCF_3, OR^{10}, COR^6, $NHCOR^7$, $NHSO_2R^9$, CN, $S(O)_pR^9$, phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^5, COR^6, CN, $NHCOR^7$ and methylenedioxo, or a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur which heteroaromatic ring may be substituted by C_1-C_6 alkyl; or R^3 and R^4 together may form a fused phenyl ring;

R^5 is independently hydrogen, C_3-C_6 alkenyl, C_3-C_6 alkynyl, or C_1-C_6 alkyl optionally substituted by hydroxy, C_1-C_3 alkoxy, NR^7R^8, phenyl optionally substituted by one or more substituents selected from halogen, C_1-C_6 alkyl, CF_3, OCF_3, CN, or a 5- or 6-membered heteroaromatic group optionally substituted by C_1-C_6 alkyl;

R^6 is C_1-C_6 alkyl, OR^5 or NR^7R^8 or phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^5, COR^6, CN, and $NHCOR^7$;

R^7 and R^8 are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl optionally substituted by one or more substituents selected from halogen, CF_3, OCF_3, OR^5, and CN, or a 5- to 10-membered mono- or bicyclic heteroaromatic ring containing up to three heteroatoms selected from oxygen, nitrogen and sulfur which heteroaromatic ring may be substituted by C_1-C_6 alkyl; or R^7 and R^8 together with the nitrogen to which they are attached may form a 5- or 6-membered ring which may contain an additional heteroatom selected from oxygen, nitrogen and sulfur;

R^9 is C_1-C_6 alkyl, or phenyl optionally substituted by one or more substituents selected from halogen, CF_3, OCF_3, OR^5, and CN;

R^{10} is hydrogen, C_3-C_6 alkenyl, C_3-C_6 alkynyl, or C_1-C_6 alkyl optionally substituted by hydroxy or C_1-C_3 alkoxy; and

p is 0, 1 or 2.

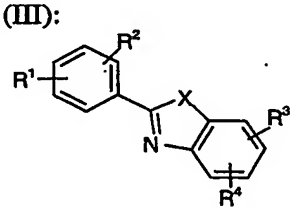
2. A compound according to claim 1 wherein X is preferably O.

3. A compound of formula (I) as described in any one of Examples 1 to 41 or a pharmaceutically acceptable salt or prodrug thereof.

4. A compound as defined in any one of claims 1 to 3 for use in medicine.

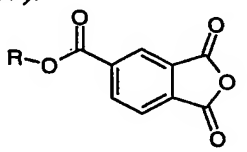
5. A process for the preparation of a compound as defined in any one of claims 1 to 3 which comprises:

a) treating a compound of formula (III):



(III)

wherein R^1 is NH_2 or a protected derivative thereof and X, R^2, R^3 and R^4 are as defined for formula (I), with a compound of formula (IV):



(IV)

wherein R is H, C_1-C_6 alkyl or a protecting group, by heating in a suitable acidic medium; or

b) heating a compound of formula (III) with a compound of formula (IV) with an organic base in a suitable solvent, followed by heating in a suitable acidic medium.

6. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 3 together with a pharmaceutically acceptable carrier or excipient.

7. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of an inhibitor of heparanase.

8. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a subject with cancer.

9. The use as claimed in claim 8 wherein the cancer is either;

(a) a metastatic tumour cell type, such as, melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, and mastocytoma; or

(b) a type of carcinoma e.g. colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer , renal cancer, gastric cancer,and ovarian cancer.

10. The use of a compound as defined in any one of claims 1 to 3, in the manufacture of a medicament for the treatment of a subject with angiogenesis or angiogenesis dependent diseases. which include angiogenesis associated with the growth of solid tumours and retinopathy.

11. The use according to claim 10 wherein the angiogenesis dependent diseases are angiogenesis associated with the growth of solid tumours and retinopathy.

12. The use of a compound as defined in any one of claims 1 to 3, in the manufacture of a medicament for the treatment of inflammatory diseases.

13. The use according to claim 12 wherein the inflammatory conditions are rheumatoid arthritis, inflammatory bowel disease, and wound healing.

14. The use of a compound as defined in any one of claims 1 to 3, in the manufacture of a medicament for the treatment of cardiovascular diseases.

15. The use according to claim 14 wherein the cardiovascular diseases are thromboembolic disease, arterial thrombosis and restenosis.